

TYGERBERG HOSPITAL IN SOUTH AFRICA; A MODEL FOR DIABETES CARE IN SUB- SAHARAN AFRICA



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1. ABSTRACT

Background: Type 1 diabetes (T1D) is the most common form of diabetes mellitus (DM) among children/adolescents under the age of 15 years. This was also the situation at the pediatric ward at Tygerberg Hospital (TH) in South Africa (SA) and at Stavanger University Hospital (SUH) in Norway. The incidence of T1D among children/adolescents is increasing in Norway, as well as in sub-Saharan Africa (SSA). If T1D is not adequately treated the patients might die of either acute- or long-term complications. Therefore it is important to work for better diabetes care in countries in e.g. SSA.

Aims: The aims of this thesis were to compare diabetes care at TH in SA to diabetes care in SSA/Africa in general, and to another public hospital, SUH in Norway. Another aim was to assess if international consensus guidelines in diabetes care were followed at TH and SUH.

Methods: A literature review on the guidelines of the International Society for Pediatric Adolescents Diabetes (ISPAD), and about T1D in SA, in SSA in general, and in Norway was performed through a search for information on PubMed. Using a standardized questionnaire based on ISPAD's guidelines diabetes care providers were interviewed at TH, and SUH.

Results: In SSA countries patients with T1D often do not receive adequate health care. Due to various reasons it seem to be impossible to achieve the ISPAD's recommendations for many health-institutions in SSA. Both TH and SUH were able to put into practice most of the ISPAD's guidelines according to diagnostics, treatment, follow-up, treatment goals, as well as screening for complications/associated autoimmune diseases. Most of the patients at TH had DKA at the time of diagnosis, while 6 % of the patients at SUH were diagnosed with DKA. None of the patients at TH were on insulin pump, while 51 % were on this treatment regime at SUH. Around 9 % of the patients at TH achieved an HbA1c < 7.5 %, while approximately 33 % of the patients at SUH achieved the treatment goal. At TH, they seldom saw patients with severe hypoglycaemia, while 9 % of the patients at SUH developed this form of acute complication. Around 16.4 % of the patients at TH developed DKA after the time of diagnosis, while 3.5 % of the patients at SUH did the same. At SUH, one patient had developed nephropathy, and one patient received treatment for hypertension (HT), and hypercholesterolemia. Unfortunately it was not possible to receive information about long-term complications among the patients at TH.

Conclusion: Diabetes care at TH in SA appeared to be well-functioning compared to the knowledge about diabetes care in SSA. Since patient data from TH for the year 2010 in total was partly missing, it was difficult to draw any firm conclusion about the quality of the diabetes care at TH compared to the diabetes care at SUH. However, based on the information received by interviewing health personnel at both places, most aspects of the diabetes care at TH were comparable to the diabetes care at SUH.

2. ABBREVIATIONS

Abbreviation	Description
AC	Albumin Concentration
ACEI	Angiotensin-Converting-Enzyme-Inhibitor
ACR	Albumin/Creatinine Ratio
ADA	American Diabetes Association
AER	Albumin Excretion Rate
AIIRA	Angiotensin II Receptor Antagonists
BG	Blood Glucose
BMI	Body Mass Index
CMR.	Child Mortality rate
CSGM	Continuous Subcutaneous Glucose Monitoring
CSII	Continuous subcutaneous insulin infusion
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complication Trial
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
ESRF	End Stage Renal Failure
GDP	Gross Domestic Product
GFR	Glomerular Filtration Rate
GP	General Practitioner
HbA1c	Hemoglobin A 1 C
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte antigen
HT	Hypertension
IDF	International Diabetes Federation
IgA EMA	Immunoglobulin A antiendomysial
ISPAD	International Society for Pediatric and Adolescents Diabetes
IZS Lente type	Insulin Zink Suspension Lente Type
LDL	Low Density Lipoprotein
MDI	Multi-daily injections
MODY	Maturity Onset of Diabetes in Young
NCDR	Norwegian Childhood Diabetes Registry
NPH	Neutral Protomine Hagedom (insulin)
OGTT	Oral Glucose Tolerance Test
SA	South Africa
SMBG	Self-monitoring of blood glucose
SSA	Sub-Saharan Africa
SUH	Stavanger University Hospital
T1D	Type 1 diabetes

Abbreviation	Description
T2D	Type 2 diabetes
T4	Thyroxine
TH	Tygerberg Hospital
TSH	Thyroid-stimulating hormone
Ttg	Tissue transglutaminase
UIO	University of Oslo
UNDP	United Nations Development Programme
USD	United States Dollar
WHO	World Health Organization

3. INTRODUCTION

Diabetes Mellitus (DM) can be defined as a group of metabolic diseases, caused by defects in insulin secretion, insulin action or both [1]. DM can be classified into various types like T1D, type 2 diabetes (T2D), MODY (Maturity Onset of Diabetes in Young), secondary diabetes (e.g. gestational diabetes), and other less common form of DM [2]. However, the majority of cases of diabetes fall into two main categories, T1D and T2D. A total of 90-95 % of the individuals diagnosed with DM, have T2D globally, while T1D accounts for 5-10 % of the cases. T1D is characterised by an absolute deficiency of insulin secretion, while T2D is caused by a combination of increasing resistance to insulin action and an inadequately compensatory insulin secretory response [3].

DM is one of the most common non-communicable diseases in the world. In 2011, a total of 366 million people had diabetes, and as many as 4.6 million deaths were attributable to DM. In most high-income countries, DM is the fourth or fifth leading cause of death. In economically developing and newly industrialized countries, information about DM is more scarce. However, it has been proved evident that diabetes is epidemic [4]. The majority of the countries in SSA can be defined as developing countries. According to the International Diabetes Federation (IDF), more than 80 % of the individuals with diabetes live in the economically less developed regions in the world. Only 20 % of the global healthcare expenditures on DM are spent in low-and middle-income countries. This reflects large disparities between low-, and high-income countries [4]. In many ways, SA is not representative for SSA, but since the country is part of SSA geographically, it was natural to assess diabetes care and T1D in SA in light of this context.

The number of individuals with T2D has, in most countries, increased due to rising rates of e.g. obesity, reduced physical activity, dietary changes, and less healthy behavior [5]. Additionally, although less common than T2D, T1D is increasing annually both in developed and developing countries [4].

The main focus in this thesis is children/adolescents with DM diagnosed under the age of 15 years. Even though reliable data are sparse, T2D in young people is increasing in some countries and in risk populations [4] [6]. However, childhood onset T1D is one of the most common endocrine and metabolic conditions in children/adolescents [4]. In most of the western countries, T1D accounts for over 90% of the cases of young people being diagnosed with diabetes [7]. Since information about T1D among children/adolescents in SSA/Africa is relatively sparse, it was difficult to find similar information about the total percentage of young people with T1D in this region. T1D appears to be a growing concern worldwide [8], and the incidence of children/adolescents with childhood onset

T1D is increasing [4]. While there has been markedly improvement in the knowledge, epidemiology and management of T1D in developed countries in the world, there have been little or no improvements in SSA, according to Majaliwa et al. [8]. Therefore, it is likely that more children are dying early due to diabetes complications in countries in SSA [8]. It is important to focus on T1D among children/adolescents in this region. The vast majority of the children and adolescents with diabetes at TH (approximately 85-90%) and SUH (>99%) had T1D. The main focus in this thesis will be childhood onset T1D.

ISPAD is an organization that works to promote “clinical and basic science, research, education and advocacy in childhood and adolescent diabetes” [9] through defining guidelines for management of diabetes amongst patients aged from 0 to 14 years. In 2009, ISPAD published an updated edition of their International Consensus guidelines concerning diabetes care. With these guidelines they hope to assist caregivers in managing children/adolescents with DM around the world, to raise awareness of the importance of access to essential resources like e.g. insulin, and to raise the knowledge of serious long-term implications of poorly managed diabetes [10]. To exemplify the importance of ISPAD’s guidelines it has been shown that the implementation of these guidelines have improved the diabetes care at hospitals in Norway [11]. It appears that no similar studies have been done in SA, but it is natural to think that implementations of these guidelines would have shown health care improvements here as well. The diabetes care at TH and SUH is based on ISPAD’s guidelines, and therefore this thesis will describe these guidelines, and how they are actually practiced at those two hospitals.

4. AIMS

The main aim of this thesis was to portray how diabetes care is organised in one public university hospital in SA, TH, with reference to the ISPAD guidelines, and to compare it to the diabetes care given at another public university hospital in Norway, SUH, and to the diabetes care given in countries in SSA in general. Even though the health care given at TH might not be representative for the health care given in SA in general, it can at least give an impression of how diabetes care might function in some regions of the country. Hopefully this thesis will contribute to increase the knowledge about T1D and diabetes care both in SA and SSA.

This thesis is also a part of a larger study called «Diabetes in children; a global comparative study». All together, 11 medical students have been part of this project, going to various countries including Canada, USA, India, Argentina, Australia, Rwanda, South Africa, and Norway to collect information about diabetes care, based on the same standardized questionnaire and observing. An

overriding aim was to make an effort to portray diabetes care in SA to later be able to compare this with diabetes care in various other countries and regions around the world.

5. METHODS

A search mainly on PubMed was performed to find relevant literature on DM, T1D in general and in children/adolescents in SSA, SA, and Norway. The keywords when searching were diabetes mellitus type 1, mortality, complications, South Africa, Africa, and Norway, and in most of the cases the searches were limited to children < 18 years. Additionally, the Diabetes Atlas published by the IDF served as an important source of information.

In an interview study, the local strategies to diagnostics, treatment, and follow up were explored, interviewing diabetes nurse Fiona Liebenberg, and paediatric endocrinologist, MD Ekkekard Zöllner at TH, and diabetes nurse Liv Haram at SUH. Additionally, data about T1D in Norway were mainly provided by the Norwegian Childhood Diabetes Registry (NCDR).

The standardized questionnaire (appendix 1) used has been developed by fellow medical students from the University of Oslo (UIO), and was mainly based on international guidelines formulated by ISPAD and American Diabetes Association (ADA). Due to practical reasons, the personnel at TH received the questionnaire one day prior to the interview, while the diabetes nurse at SUH was presented to the questionnaire the same day she was interviewed. Diabetes nurse Fiona Liebenberg and Doctor Ekkekard Zöllner were interviewed in January 2011, and diabetes nurse Liv Haram at SUH was interviewed in December 2010. It was only possible to be present at TH and SUH during short periods. Thus, the information about diabetes care at TH and SUH is mainly based on the data received from the personnel at the two hospitals, not by personal observations. The health personnel at the pediatric ward at TH first started register patient data in August 2010. Therefore, the patient data received was from the period between August and December 2010, and not from the year 2010 in total, like at SUH. Additionally, patient data from SUH for the year 2011 has been collected from the NCDR.

6. PART 1 and PART 2: LITERATE REVIEW

6.1. PART 1: TYPE 1 DIABETES MELLITUS

T1D can be defined as an autoimmune disease, and is due to selective destruction of the B-cells producing insulin in the pancreas. This is usually leading to absolute insulin deficiency [12]. Individuals with T1D are more prone to develop diabetes ketoacidosis (DKA) [7] and need daily

administration of insulin [13]. Patients with T1D have a risk of injecting too much insulin compared to their needs in a specific situation. This can result in hypoglycaemia [14]. Chronic hyperglycaemia is a consequence of uncontrolled diabetes, and is associated with long-term complications in various organs like the kidneys, eyes, nerves, heart, and blood vessels, such as nephropathy, neuropathy, retinopathy, and macrovascular disease. Patients with T1D have an increased risk of developing other autoimmune disorders, such as e.g. hypothyroidism, hyperthyroidism, and celiac disease [1].

6.1.1 Incidence and prevalence of children/adolescents with type 1 diabetes in a global perspective

IDF estimated that the total number of children and adolescents under the age of 15 years was 1.9 billion in the world in 2009, 480 000 of them living with T1D [4]. According to IDF, the number of young people developing T1D is increasing rapidly in many countries, especially in those under the age of 15 years [4]. Based on two major studies on incidence of childhood onset T1D [15, 16], IDF concluded that 76 000 young people aged between 0 and 14 years are developing T1D worldwide annually. It appears to be geographic differences in trends, but the overall annual increase is estimated to be nearly 3 %. However, in sub-Saharan Africa incidence data are sparse or non-existent [4].

According to IDF the number of European children and adolescents with T1D is 116 100 with 17 900 newly diagnosed cases per year. In the African region, IDF has estimated that a total number of 36 100 individuals aged between 0 and 14 years have T1D in 2011, and that 5 900 children/adolescents are diagnosed with childhood onset T1D every year [4].

6.1.2 Etiology and pathogenesis of childhood onset type 1 diabetes

T1D are as mentioned mostly due to cell mediated destruction of the insulin-producing B-cells in the endocrine pancreas [1]. T1D becomes clinically symptomatic when approximately 90 % of these cells are destroyed [7]. Serological markers or antibodies of this autoimmune destruction can be detected in 85-90 % of the individuals with T1D. Additionally, T1D is strongly associated with Human leukocyte antigen (HLA). The various HLA-alleles can either be predisposing or protective against T1D. The B-cell destruction can be explained by multiple genetic factors [1]. However, the constantly increasing incidence of T1D during the last 10-13 years cannot be explained by shifts in genetic susceptibility alone [15]. Studies indicate that rapid growth and obesity in early childhood increases the risk of developing T1D [17], and that psychological stress in families is associated with diabetes-associated autoantibodies in one-year-old children [18]. Environmental factors [19-22]

seem to have a stronger effect on genetically non-susceptible individuals than on those genetically susceptible [16].

6.1.3 Diagnostic criteria for diabetes mellitus in children and adolescents

Characteristics symptoms of diabetes in children are polyuria, polydipsia, blurring of vision, weight-loss, glycosuria and ketonuria [7]

The ISPAD's diagnostic criteria for diabetes in children and adolescents are based upon the World Health Organization (WHO) report from 1999 [23] and the guidelines from ADA [3]. The diagnostic criteria for diabetes are based on the blood glucose (BG) measurement, and additionally the presence or absence of mentioned symptoms [7]:

Table 1. The International Society for Pediatric and Adolescents Diabetes's (ISPAD) diagnostic criteria for diabetes

Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/l (200 mg/dl)*. Casual is defined as any time of day without regard to time since last meal.
Or
Fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl) +. Fasting is defined as no caloric intake for at least 8 h.
Or
2-hour postload glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by WHO [23], using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g [24].

* Corresponding values (mmol/L) are ≥ 10.0 for venous whole blood and ≥ 11.1 for capillary whole blood and ± 6.3 for both venous and capillary whole blood (1).

6.1.4 Treatment of children and adolescents with type 1 diabetes

Administrations of insulin

Insulin can be administered by using different equipment such as syringes, pens, and pumps among other modalities (subcutaneous indwelling catheters and automatic jet devices). Pen injector devices have been designed to make insulin injection easier and more flexible. They contain insulin in prefilled cartridges which eliminate the need for drawing up insulin from a vial. The dose is dialed up on a scale and they may be particularly useful for administration of insulin away from home [25]. Continuous subcutaneous insulin infusion (CSII) is frequently called insulin pump therapy. This is according to ISPAD the best way of imitating the physiological insulin profile. The basal rate of

insulin is preprogrammed, and insulin is infused subcutaneously. In addition boluses are added to counterbalance the intake of carbohydrates [25].

The disadvantage concerning both pen injector devices and pumps is that it is a more expensive method of administering insulin compared to conventional syringes. Thus, it is not always available in every country [25].

Different types of insulin

Insulin can be divided into different groups according to their onset and duration of action (table 2). According to ISPAD children and adolescents with T1D should at least have access to adequate amounts of regular and intermediate-acting insulin (Neutral Protamine Hagedom insulin (NPH)) since they are dependent on insulin for survival [25]. It has been shown that insulin analogues reduce the risk of hypoglycemia in adolescents [26]. ISPAD recommends using this type of insulin in a treatment regimen.

Table 2. Insulin can be divided into different groups according to their onset and duration of action;

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid acting analogues (aspart, glulisine, lispro)	0.15-0.35	1-3	3-5
Regular/soluble (short acting)	0.5-1	2-4	5-8
Intermediate acting			
Semilente (pork)	1-2	4-10	8-16
NPH*	2-4	4-12	12-24
IZS Lente type*	3-4	6-15	18-24
Basal long-acting analogues			
Glargine	2-4	None	24**
Detemir	1-2	6-12	20-24
Long-acting			
Ultralente type	4-8	12-24	20-30

* NPH = Neutral Protamine Hagedom insulin; IZS, insulin zinc suspension.

** The duration of action might be shorter than 24 hours [27].

Treatment-regimens

According to ISPAD many factors influence on which insulin regimen is the most suitable for a patient. Age, diabetes duration, lifestyle (diet, physical activity, school, type of work), and the

patient/family's preferences play important roles [25].

In their guidelines, ISPAD describes the three most frequently used regimens, a two or three injections regimen or a basal bolus regimen [25];

1. Two injections daily consisting of a combination of short- or rapid- and intermediate-acting insulin (one injection before the breakfast and one injection before the main evening meal).
2. Three injections daily consisting of a mixture of short- or rapid- and intermediate-acting insulin before breakfast. Then rapid or regular insulin can be given alone before the afternoon snack or the main evening meal and intermediate-acting insulin before bedtime or a variation of this.
3. A basal-bolus regimen implies an intermediate-acting insulin or basal/long-acting analogue at bedtime or two times per day (during mornings and evenings), in addition to injection of a rapid-acting analogue/regular insulin before every meal. Regular insulin should be given 20-30 minutes before each main meal. 40-60% of the total daily insulin requirements should be basal insulin, while the rest should be pre-prandial rapid-acting or regular insulin.

According to ISPAD the basal-bolus regimen has the best ability to imitate the physiological insulin profile. CSII is often used within this regimen [25]. Randomized trials have shown that better BG control has been obtained when using multi injection therapy (MDI) and pumps compared to a twice daily treatment [28, 29]. The Diabetes Control and Complications Trial (DCCT) has also proved that intensive insulin therapy including a heavy multidisciplinary approach in adolescents resulted in a decreased number of long-term complications [29]. Based on the results of various randomized trials ISPAD now recommend four or more injections per day.

Treatment targets

The treatment targets is to obtain a level of BG that is as close to the normal range as possible (3.0-5.5 mmol/L) [30]. To achieve this, it is necessary with daily self-monitoring of blood glucose (SMBG), periodic monitoring of long-term concentration of glucose (Hemoglobin A1c (HbA1c)) and intensive insulin treatment. Monitoring of the HbA1c has been shown to be the most useful measure in evaluating metabolic control [29], and it is an indication of the average BG- level of the preceding 10-12 weeks [31]. A limitation of HbA1c is that it does not take into account fluctuations in the blood sugar, which can play a role in development of complications [32]. The DCCT, and similar studies have provided clear evidence that better metabolic control, as measured by a lower level of HbA1c, is associated with fewer and delayed microvascular complications [29, 33]. The DCCT showed that a 2 % increase in the HbA1c- level could explain 96% of the complications [34].

Frequent measurements of BG are associated with improved HbA1c [35]. To optimize each child's diabetes control ISPAD recommend that the BG should be measured 4-6 times per day. The cost of BG monitoring is however very expensive, and the technology can be unavailable in many countries [36].

ISPAD recommend that the treatment goal of HbA1c should be less than 7.5 % for all children and adolescents under the age of 18 years. How often HbA1c is measured depends on the local facilities and availability. As a minimum, every child should have at least one measurement per year according to ISPAD. Ideally, the HbA1c should be measured four to six times per year in younger children and three to four times per year in older children [36].

6.1.5 Diabetes complications in children and adolescents with focus on T1D

Acute complications

Diabetic ketoacidosis

Diabetes ketoacidosis (DKA) is the result of a combination of absolute or relative lack of insulin and increased levels of counterregulatory hormones such as catecholamines, glucagon, cortisol and growth hormone [37, 38]. This lead to an accelerated catabolic state with increased glucose production in the liver and kidney, impaired utilization of peripheral glucose resulting in hyperglycemia and hyperosmolality, and an increased breakdown of lipids and production of ketone bodies, which lead to ketonemia (elevated level of ketone bodies in the blood) and metabolic acidosis [39].

Table 3. The International Society for Pediatric and Adolescents Diabetes's (ISPAD) diagnostic criteria for Diabetes Ketoacidosis are [39];

1. Hyperglycemia (blood-glucose > 11 mmol/L)
2. Venous pH < 7.3 or bicarbonate < 15 mmol/L
3. Ketonemia and ketonuria

The clinical manifestations of DKA are dehydration, rapid and deep sighing (Kussmaul respiration), nausea, vomiting, abdominal pain mimicking an acute abdomen, progressive obtundation and loss of consciousness, increased leukocyte count with left shift, non-specific elevation of serum amylase, and fever when infection is present [39]. ISPAD has defined their diagnostic criteria for DKA (table 3).

Hypoglycemia

Hypoglycemia is one of the most frequent acute complications due to the treatment of T1D, and it is a result of a mismatch between the insulin dosage, food intake, and recent exercise [14].

For clinical use, a BG-value of less than 3.6 mmol/L has often been used as the level for defining hypoglycemia in children and adolescents [14]. However, based on a report published by ADA Working Group, ISPAD recommend that the treatment goal should be above 3.9 mmol/L [14].

Hypoglycemia can be accompanied by various sign and symptoms of neurological dysfunction and/or autonomic activation, such as poor judgment and confusion, problems with short-term memory, blurred vision or double vision, difficulty concentrating, and pounding heart among other symptoms. It may also result in behavioral or mood changes in form of irritability, erratic behavior, inconsolable crying and nightmares. In rare cases hypoglycemia can lead to permanent long-term sequelae due to loss of consciousness, or repeated episodes of seizures. Hypoglycemia is also potentially life-threatening [14].

Late complications

Patients with chronic hyperglycemia over time can develop long-term microvascular complications such as retinopathy, nephropathy, neuropathy and macrovascular disease. Diabetic retinopathy can lead to reduced vision and blindness. Diabetic nephropathy can cause renal failure and HT. Individuals with diabetic neuropathy can develop muscle weakness, pain, paresthesia and autonomic dysfunction. Cardiac disease, stroke, peripheral vascular disease and amputation of the limbs can be a consequence of macrovascular disease due to diabetes [40].

Other risk factors for developing long-term complications are long duration of diabetes, older age and puberty [41], smoking [42-44], HT [45, 46], dyslipoproteinaemia [47, 48], family history of complications [49, 50], little physical activity [51] and higher Body Mass Index (BMI) [52, 53].

Microvascular complications

Diabetic retinopathy

Adolescents with T1D have a higher risk of developing vision threatening retinopathy compared to adult patients [54, 55]. Diabetic retinopathy can develop rapidly, particularly in patients with unsatisfactory glycaemic control [56]. Screening of adolescents for early signs of retinopathy and risk factors should therefore be performed [40].

Screening for retinopathy

ISPAD has formulated the following recommendations in their guidelines;

1. Screening for retinopathy (and microalbuminuria) should be performed from the age of 11 years when the patient has had diabetes for two years or from nine year of age when the child or adolescent has had T1D for five years all together [57].
2. Screening for retinopathy should as a minimum include ophtalmoscopy through dilated pupils by an experienced observer [40].
3. In general, screening for retinopathy should occur annually. If the patient has high risk features for developing visual loss, the screening should be performed more frequently than every year [54].

Diabetic nephropathy

Persistent proteinuria greater than 500 mg/24 hours or albuminuria greater than 300 mg/24 hours in two out of three consecutive urines is the definition of diabetic nephropathy. This is normally also associated with HT, and a reduced glomerular filtration rate (GFR) [58]. When a patient has had diabetic nephropathy over a long period it can progress to End-stage renal failure (ESRF) which requires dialysis or kidney transplantation. Diabetic nephropathy is an important cause of mortality and morbidity amongst young adults with T1D [59]. To prevent development of an ESRF in children/adolescents and adults with early onset diabetes it is important to detect diabetic nephropathy at an early stage and to ensure a satisfactory treatment of an elevated blood pressure [60].

The first clinical sign of incipient nephropathy is microalbuminuria [40], and this is defined as any of those below [58]

1. Albumin excretion rate (AER) between 20 and 200 mikrogr/min or AER 30-300 mg/24 h in urine collected during the last 24 hours (Timed urine collections).
2. Albumin concentration (AC) 30-300 mg/L (early morning urine sample)
3. Albumin/creatinine ratio (ACR) 2.5-25 mg/mmol or 30-300 mg/gm (spot urine) (males), and 3.5-25 mg/mmol (females).

Screening for nephropathy

ISPAD recommends annually screening for microalbuminuria using any of the methods mentioned (AER, AC, ACR) [57] (table 4).

Diabetic neuropathy

Both the somatic and the autonomic nervous system can be affected when a patient has had uncontrolled diabetes over time. Somatic neuropathies can be divided into two main categories, namely focal neuropathies where only one specific nerve is affected, and sensorimotor polyneuropathy, where multiple nerves have been affected [40]. Autonomic neuropathy can cause different symptoms, such as e.g. diarrhoea, vomiting, paresis of the bladder, and impotence among others [61].

Screening for neuropathy

Diabetic neuropathy is a seldom complication of T1D amongst children and adolescents. Hence, ISPAD has not formulated any recommendations when it comes to screening of neuropathy [40].

Macrovascular disease

Compared to individuals without diabetes, the mortality and morbidity of cardiovascular disease (CVD) are markedly increased in individuals with diabetes [62]. Patients with T1D whom are smoking [40], and who have a family history of; early CVD (before the age of 55), disturbances in the lipid status, T2D, and HT [63] have an increased risk of developing macrovascular disease.

Screening for macrovascular disease

As a minimum, ISPAD recommend that the blood pressure should be measured annually. The blood pressure value should be compared with age-appropriate centile charts, and it should be maintained on a level less than the 95th centile for the specific age group [64]. Both ISPAD and ADA recommend that screening for fasting blood lipids should be performed soon after diagnosis in all patients under 12 years of age with T1D. If the values are within the normal range, it is only necessary to repeat it every five years. If the patient has any family history of hypercholesterolemia or has any other risk factors of developing macrovascular disease, the screening should be performed already from the age of two [65]. The concentration of low-density lipoprotein (LDL) cholesterol should be lower than 2.6 mmol/L [40].

Screening for late complications

ISPAD recommend the following screening-program for late complications (table 4) [40]:

Table 4. Screening, risk factors and interventions for vascular complications among children and adolescents with type 1 diabetes recommended by International Society for Pediatric and Adolescents Diabetes (ISPAD)

	When to commence screening?	Screening methods	Risk factors	Potensial intervention
Retinopathy	Annually from age 11 years with after 2 years duration and from 9 years with 5 years duration	Fundal photography or mydriatic ophtalmoscopy (less sensitive)	Hyperglycaemia High blood pressure Lipid abnormalities BMI*	Improved glycaemic control Laser therapy
Nephropathy	Annually from age 11 years with 2 years duration and from 9 years with 5 years duration	Urinary albumin/creatinine ratio or first morning albumin concentration	High blood pressure Lipid abnormalities Smoking	Improved glycaemic control ACEI** and AIIRA*** Blood pressure lowering
Neuropathy	Unclear	History and physical examination	Hyperglycaemia Higher BMI	Improved glycaemic control
Macrovascular disease	After age 12 years	Lipid profile every 5 years, blood pressure annually	Hyperglycaemia High blood pressure Lipid abnormalities Higher BMI Smoking	Improved glycaemic control Blood pressure control Statins

*BMI; Body Mass Index, **ACEI; Angiotensin-Converting-Enzyme Inhibitor, ***AIIRA; Angiotensin II Receptor Antagonist

Associated autoimmune conditions

Hypothyroidism

Common symptoms of hypothyroidism are increased weight gain, retarded growth, tiredness, lethargy, cold intolerance and bradycardia [66].

Hypothyroidism is confirmed by detecting a low free thyroxine (T4) and a raised Thyroid-stimulating hormone (TSH) concentration in the blood. An individual with a subclinical condition have a normal level of T4, and a modestly increased TSH [66].

Hyperthyroidism

Symptoms and signs of hyperthyroidism can be unexplained difficulty in maintaining glycaemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement, and/or characteristic eye signs (exophtalmus) [66].

Celiac disease

Celiac disease is in many cases asymptomatic [67], but it can also lead to symptoms like diarrhea, abdominal pain, flatulence, dyspeptic symptoms, recurrent aphthous ulcerations, unexplained poor growth and/or anemia [68].

Detection of IgA (Immunoglobulin A) antiendomysial (EmA) antibodies and IgA antibodies against tissue transglutaminase (tTG) indicates that a person has celiac disease [69]. When screening for celiac disease, it is important to exclude IgA deficiency to avoid a false negative test [70].

Screening for autoimmune associated conditions

As long as a patient with T1D do not have symptoms of celiac disease, do not have goiter, or as long as thyroid antibodies are absent, ISPAD recommend that screening of thyroid function should be carried out at the time of diagnosis of diabetes, and every second year thereafter. More frequent controls are necessary if otherwise [66].

Further, ISPAD recommend that screening for celiac disease should be performed at the time of diagnosis, annually for the first five years, and every second year thereafter. If the child/adolescent has symptoms of celiac disease, or if he/she has a first-degree relative with the disease, an assessment should be carried out more frequently [66].

6.1.6 Diabetes education in children and adolescents

ISPAD`s guidelines claim that "education is the keystone of diabetes care and structured self-management education is the key to a successful outcome" [71]. According to DCCT and other studies a frequent and high level of educational input and continuing support are essential to obtain an effective, and intensive self-management of diabetes, which in many cases can prevent development of diabetes related complications [29, 72].

In the guidelines from 2009, ISPAD has listed up five different aspects that should be included in a structured educational programme based on research that has been conducted by various organizations. It has been recommended that [73, 74];

1. Diabetic education should be available to all individuals with diabetes at the time of diagnosis, or when it is appropriate for them, and it should be given on an on-going basis as required. The educational training should be individualised as good as possible.
2. A trained interdisciplinary team should provide the education.
3. This educational team should at least include a diabetes specialist nurse and a dietician.

4. The diabetic education needs to be held in a location where the patients and their families have the opportunity to meet up, either in their community or at the inpatient centre.
5. The educational team should use a variety of teaching techniques, and the training should be adapted as well as possible to the children/adolescents and their parents.

ISPAD divide the educational training into a primary level at the time of diagnosis and a secondary level including continuous training after diagnosis. Through primary education the patients e.g. learn about diabetes, the mechanism behind the disease, are trained in practical skills, receive basic dietetic advices, learn about normal BG levels and glucose targets, learn about the importance of treatment with insulin, and how to avoid acute complications. The secondary education is more or less a continuation of the primary education [75].

6.2. PART 2: DIABETES IN A GLOBAL PERSPECTIVE WITH FOCUS ON SUB-SAHARAN AFRICA AND SOUTH AFRICA AND NORWAY

6.2.1. Part 2a. Background information about South Africa and Norway

South Africa (SA), officially called the Republic of South Africa, is situated in the very south of the African continent. Namibia, Botswana, Zimbabwe, Mozambique, Swaziland and Lesotho constitute the neighbouring countries. SA had a population of 50.59 million people in 2011 [76]. This makes it one of the most populous countries in Africa [4]. During the period between 1948 and 1994, the National Party was the ruling party in SA, and during this time the country was under an Apartheid regime where racial segregation was legislated by law. The South African population was classified into four racial groups, namely the “black/native”, “white”, “colored”, and “Asian”. The “white” individuals were looked upon as superior to the other groups by the government, being treated thereafter.

SA has 11 official languages. Zulu is the most common language spoken at home by South Africans (24 %), followed by Xhosa (18 %), and Afrikaans (13 %). English is the dominant language used in media, and in government, and it is understood in most urban areas. However, it is only the sixth-most common language spoken at home [77]. According to WHO the literacy rate among adults aged ≥ 15 years in SA was 89% in 2008 [78].

The prevalence of individuals infected by Human Immunodeficiency Virus (HIV) was 10.6 % of the total South African population in 2011[76]. This poses a major health challenge to SA. Additionally, it has been shown that HIV, and some of the antiviral drugs used in the treatment of

patients with HIV, can cause the metabolic syndrome which can lead to development of diabetes or deterioration in glycemic control in already diagnosed diabetes patients [79].

Norway is part of Scandinavia (Finland, Norway, and Sweden) situated in Northern Europe. Approximately five million people live in Norway [80]. The Norwegian language has two official written forms, bokmål and nynorsk, and both of them are recognized as official languages in the country. However, bokmål is used by the majority of the people, namely around 80-85 %. The majority of the people (95 %) speak Norwegian as their native language. The Sami population constitute one of the ethnical minority groups in Norway, having a Sami language as their main written and spoken language. However, in the majority of cases, they can understand Norwegian. Since all school children learn to write and speak English as the main foreign language at an early age most of the Norwegians speak fluently English at an older age. Due to an increasing number of immigrants to Norway, and especially to the larger cities, communication can be a challenge e.g. in the health sector if the immigrants do not understand either Norwegian or English. The literacy rate in Norway is approximately 99 %.

It has been estimated that around 3500 to 4000 individuals live with an HIV-infection in Norway in 2011 [81].

The Human Development Index (HDI) reflects the level of development in a specific country. The HDI is based on three basic dimensions of human development, such as health, education and income. According to the report being published by the United Nations Development Programme (UNDP) in 2011, SA had a HDI of 0.619, which gives the country a rank of 123 out of 187 countries in total. The average level of HDI in SSA is today 0.463, and this places SA above the regional level [82]. Norway has a HDI of 0.943 which gives the country a rank of 1 out of 187 countries. The average HDI in the region which Norway is a part of is 0.873 [82].

In SA, the Gross domestic product (GDP) was calculated to be US \$ 408 billion in 2011 [83]. In 2010, the total expenditure on health was approximately 8.9 % of their GDP [78]. The country's spending on health exceeds that of the majority of the other countries in SSA. For comparison Mozambique, Botswana, and Namibia spent 5.2 %, 8.3 %, and 6.8 % of their GDP on health, respectively [78]. In 2011, it was estimated that Norway had a GDP of 486 billion US \$ [83]. In 2010 Norway spent 9.5 % of their GDP on health services [78].

Additionally, the life expectancy rate and the infant mortality rate can reflect the degree of development in a certain country. In 2011, the life expectancy rate was estimated to be 54.9 years for males, and 59.1 years for females in SA. The infant mortality rate was calculated to be 41 out of 1000 live births in 2010 [78]. The same year, the infant mortality rate in Norway was estimated to be 3 out of 1000 live births [78], and the life expectancy rate was calculated to be 81.1 years [82]. When it comes to the child mortality rate (CMR) approximately 12 % of the children in SSA die before the age of five years. For comparison, 5.7 % of the children in SA die before their fifth birthday [78]. In 2009, approximately 13.8 % of the South African population were living on < one dollar per day, while none of the inhabitants in Norway was forced to do the same [78].

6.2.2. Part 2b. Diabetes mellitus in Africa, with focus on Sub-Saharan Africa and South Africa

In 2011, IDF published an article named “Africa’s silent epidemic”. IDF claimed that more than 78% of the people living with diabetes in Africa were undiagnosed. They also estimated that around 14.7 million had diabetes (T1D and T2D) in Africa in 2011, and according to them this number will increase to 28 million by 2030, around a 90 % increase. The majority of this group is under the age of 60 years. This entail an even greater challenge since those people are in the most productive years. After Nigeria, SA has the second largest number of people with diabetes (T1D and T2D) in Africa, estimated to be 1.9 million people in 2011 [4]. In 2011, the IDF published a report about diabetes in the world which showed large discrepancies between the African and the European region when it comes to the total spending on healthcare due to diabetes. IDF estimated that the African Region spent a total of 2.8 billion United States Dollar (USD) [4] while the European Region spent a total of USD 131 billion on diabetes care [84]. In fact, the statistical data showed that the African Region had the lowest total healthcare expenditures due to diabetes of any of the IDF Regions [4].

Many countries in SSA have to face health challenges due to HIV, malaria and tuberculosis. These countries where infectious diseases have traditionally dominated the health systems now face a double burden of disease [85]. This is also representative for the situation in SA. This situation entails large challenges to the health sector of resource-poor countries, because they now need to invest in systems and training of health care personnel to manage chronic diseases, such as diabetes. In addition they need to provide adequate care and appropriate medicines to people diagnosed with e.g. diabetes [86]. Even SA, which spent a larger percentage of their GDP on health than the majority of the other African countries, has a problem of achieving adequate health care for everyone. Compared to Namibia and Botswana, SA has a higher mortality rate, even though Namibia and Botswana spent a smaller percentage of their GDP on health care. This can partly be

explained by the number of people being diagnosed with HIV, Aids, and tuberculosis in SA [87].

6.2.2.1 Epidemiology of childhood type 1 diabetes in sub-Saharan Africa and South Africa

It has been estimated that the incidence of T1D amongst children/adolescents in Tanzania was 1.5 per 100 000 [88]. In Sudan, it has been reported that the incidence increased from 9.5 per 100 000 in 1991 to 10.3 per 100 000 in 1995 [89]. For comparison, a Finish study showed that the overall-age adjusted incidence was 36.5 per 100 000 [90]. In the two other Scandinavian countries, Norway and Sweden, a very high incidence ($\geq 20/100\ 000$ per year) was reported. The Scandinavian countries have the highest incidence of childhood onset T1D in the world [90].

According to published studies, the prevalence of T1D amongst schoolchildren is 0.33 per 1000 individuals in Nigeria [91], and 0.95 per 1000 people in Sudan [92]. Even though the exact prevalence of diabetes in SA is unknown, it has been estimated that around 5-7% of the population has T1D [93].

Clinically studies which has been done in SA [94, 95], Tanzania [96, 97], and Ethiopia [98] show that the age at onset of T1D is later in African communities (age 22-29) than in European populations [94-96, 98]. To exemplify, the peak age in the South African study was 24 years in males and 22 years in females, compared with a median age of 12 years in a matched group of white patients of European origin [95]. It was 20-25 years in Ethiopia [98] and 15-19 years in Tanzania [96].

6.2.2.2 Diabetes complications of childhood onset type 1 diabetes in sub-Saharan Africa and South Africa

During the period between 1982 and 2002 the first long-term outcome study on T1D alone was performed in SSA, and this was conducted in SA. Among those who survived, the study group found a statistically significant increase in rates of retinopathy and HT, but not of other diabetes complications [99].

In a Tanzanian study, they concluded that the rate of both acute and chronic complications was high. A total of 75 % of the patients presented with DKA at the time of diagnosis, 89.8 % had at least one episode of DKA, while approximately 55.7 % had symptomatic hypoglycaemic episodes. Additionally the study showed that microalbuminuria was presented in 29.3 % of the children/adolescents with T1D, and retinopathy in approximately 22.7 % of the patients participating [100]. In a Congolese study they found that 18.3 % of the children/adolescents with

DM had DKA at the time of diagnosis, and a total of 79.3 % of the patients developed DKA during an observation period of ten years [101]. In 2002, results from another Tanzanian study including both young and adult patients with T1D, or T2D aged between 4 to 88 years, were published. Out of all the individuals participating, 15 % were classified as having T1D. Among all the patients (with T1D or T2D, around 10 % were not classified) the study group reported that retinopathy was found in 14 % of the individuals, foot-ulcers in 10 % of the participants, and nephropathy in 7.5 % of the patients [102].

Results from another Congolese study showed that the prevalence of microalbuminuria and macroalbuminuria among patients with T1D under the age of 30 years was 21.9 %, and 7.3 % respectively, and the percentages were highest among individuals aged above 18 years with a diabetes duration of more than five years [103].

6.2.2.2 Mortality of childhood onset type 1 diabetes in sub-Saharan Africa and South Africa

DM is an important cause of morbidity and mortality in the African region [104].

According to ADA, a total of 2.2 % of the males and 2.5 % of the females in Africa died due to diabetes in 2000 [105]. In 2010, it was estimated that around six % of the total number of deaths in SSA were attributable to diabetes. The number of deaths due to diabetes had increased from 2.2 % in 2000 to 2.5 % in 2010 [106]. The highest absolute and relative mortality rates are found in the age-group between 20 and 39 years [106].

In SSA, the South African longitudinal study mentioned is the only one which has tried to assess mortality in patients with T1D alone. The mortality rate was estimated to be 43 % among those patients whom the study group had accurate information. This study showed that most of the patients died as a result of renal failure related to diabetic nephropathy (nine out of 21 patients), six patients died because of hypoglycaemia and two persons died because of DKA. Two of the individuals died because of infection, and the reasons for death in two cases were undetermined [99].

6.2.2.4 Challenges concerning diabetes care in sub-Saharan Africa/Africa

Even though one can find little epidemiology data about T1D in SSA [4], the information that is available, show a prevalence which is much lower than in temperate countries. This is due to three factors, such as a lower incidence, that the disease is under-diagnosed and misdiagnosed, and that the patients have a poorer prognosis [86]. A study from Tanzania showed that 21 of 199 patients who got the diagnosis cerebral malaria, actually had pre-coma or coma caused by uncontrolled

diabetes [107].

At present time, insulin is still not sufficiently available in many developing countries in SSA and in Africa as a whole [108-110]. In 2006 IDF published a report concerning cost and availability of insulin in 35 countries situated in seven different IDF regions. They concluded that Africa had the lowest level of access to insulin for patients with T1D compared to the other regions included. Around 50 % of the African countries which participated in the survey claimed that people with T1D only had access to insulin in less than 50 % of the time. Mali was the only African country reporting that patients with T1D only had access to insulin in less than 25 % of the time [111]. The IDF report showed that the cost of insulin was one of the main reasons for inadequate access to insulin in most of the African countries participating in this study. The average price per 10 ml vial of insulin in the public sector in the African region was approximately 12.5 USD \$, with a variation from 2.50 USD \$ in all sections (public, private, and voluntary organizations) in Senegal to a maximum price of 34 USD \$ in the public sector in Congo. For comparison the average price for 10 ml vial of insulin was 16.5 USD \$ in the European region (from 0 USD \$ to 42 USD \$) [111]. Even though many children/adolescents with T1D still do not have sufficient access to insulin in SSA and Africa today, the focus towards access to medicines has increased considerable during the recent years. To exemplify, 39 pharmaceutical companies in SA worked for making medicines available for more patients in the country. This resulted in that the government had the right to import generic versions of patented medicines (which were less expensive), and the generics drugs could now be manufactured locally [112].

According to various studies [111, 112] it is not only limited access to insulin which is the reason for unsatisfactory diabetes care for patients in resource-poor countries or regions. Access to syringes and equipment to monitor the BG-level is essential for a patient with T1D. According to Beran et al. this is rarely available in the public sector in Mali, Mozambique, and Zambia. Thus the patients have to purchase it from the private sector, where taxes are normally added to the price, and this increases the cost even more [112]. The price of the syringes varied from US \$ 0.04 in Mozambique to US \$ 1.50 in Zambia [113]. In Mali, the average monthly spending on diabetes care for a patient including BG- testing, insulin, and transport costs was estimated to represent almost 70 % of the mean income [113]. In the Democratic Republic of Congo, the cost of diabetes care (insulin, syringes, and BG-monitoring) during one year was posing over half of the GDP per capita (income per person). In many of the African countries participating in the IDF survey, this figure was above 30 %, where insulin was the largest expenditure [111]. Partly due to the high cost of insulin and essential equipments, the life expectancy of a child with early onset diabetes might be as short as

one year in many countries in SSA [114, 115]. The median life expectancy of a child with diabetes in Bamako, the capital of Mali, has been estimated to be eight years [116], and as low as seven months in rural parts of Mozambique [113].

Additionally, it is essential to have access to diagnostic tools to be able to set the diagnosis of T1D, and to be able to monitor the BG and to adjust the treatment accordingly to the BG-level. Beran et al., found that there was a lack of such equipment in both Mozambique, Zambia, and Mali. To exemplify, it appeared that only 21 % of the health facilities included in the survey in Mozambique had a BG-metre [113]. According to Jean Claude Mbanya et al., there is still no information available whether the HbA1c is being used as a diagnostic technique for diabetes in SSA in 2010 [117].

The number of screen-detected diseases in surveys can in some way portray the availability of health care facilities for detection and treatment of diabetes in a community [106, 118]. In most of the studies from SSA, less than 50 % of the participants knew that they had diabetes from before. However, more than 50% knew that they had diabetes in urban parts of SA [119, 120], which is comparable with findings in developed countries. This can be interpreted as a sign of better health care facilities and availability of opportunistic screening in SA. By contrast, among people living in more rural areas [121] only 15 % have documented diabetes, indicating that there is a disparity in access to health care between rural and urban areas.

According to some studies which have been done in Africa, the major concern in patient care is the lack of follow up [122-125]. Access to health care workers with appropriate training is a central part of care for patients with chronic conditions such as diabetes. Beran et. al., found that there were only two doctors specialised in diabetes in each of the countries which were included in the survey, and only five to ten health care workers had received some form of training in diabetes management [112]. It seems to be an unequal distribution of health care workers between countries in SSA. Out of 150 registered diabetes educators in continental sub-Saharan Africa, 100 of them are located in SA [104]. According to IDF the “understanding of diabetes management is generally poor among health care workers, especially those in rural areas in Africa” [106].

6.2.3 Public health and diabetes care in South Africa

6.2.3.1 The public health system in South Africa

Approximately 85% of the total population in SA receive their health care from the public health sector and 15 % are funded by private health insurance. Around seven million people receive health insurance cover from more than 200 medical insurance companies (medical schemes) [93].

The health system in SA consists of a public sector and a private sector. When it comes to the public sector it is the National Department of Health that is responsible for the national health policy in the country. SA is divided into nine provincial departments of health. Within the framework of national policy and public health service delivery they have the responsibility of developing the policy in the various provinces. The public sector is today organised into three tiers of hospitals, the tertiary-, the regional- and the district-hospital. The primary health care system is mainly driven by nurses in clinics. It includes the district hospital and the community health centres. Private hospitals together with the General Practitioners (GP) constitute the private health system. In the year 2008, 70% of the private hospitals were situated in three of the total of nine provinces in the country, which might portray economical discrepancies between the regions. The private hospitals are first of all funded by medical schemes [126].

According to doctor Zöllner at TH, the public health care system finance the costs associated with diabetes medication and equipment. Both insulin, antidiabetic drugs and glucagon is 100 % financed. Materials including syringes, needles, insulin pen, home blood glucose meters, blood glucose test strips, finger-pricking devices, and urine sticks to check for ketonuria are also financed by the public health sector. If the child is under five years of age, the parents do not need to pay anything for the medication and the equipment. However, if the child is older than five years, the parents have to pay for the health care. How much they have to pay for the diabetes care depends on whether the parents have a job or not, and the income of the parents [127].

6.2.3.2 Patient organizations in South Africa

Diabetes in South Africa is a national non-profit patient organization and a member of the IDF. Through their work they want to inform, educate, empower and encourage children and their families to make them capable of taking control of their own disease. The organization is striving to work for better facilities and for improved and affordable treatment for every person with diabetes [128]. Currently there is no national diabetes registry in SA [127].

6.2.3.3 Tygerberg Hospital in South Africa

TH is situated in the Western Cape Province. It is a public and teaching hospital cooperating with the University of Stellenbosch's Health Science Faculty. The aim of TH is to provide affordable high quality health care to both public and private patients within available resources. TH is categorized as a tertiary hospital, and it is considered to be the second largest hospital in SA, and the largest hospital in Western Cape [129]. Approximately 10.5 % of the total population in SA lives in Western Cape [76], and this makes the region the fifth largest province in the country. Compared to other provinces in SA, Western Cape has the highest life expectancy at birth for both males and females [130].

More than 90 747 patients are admitted as patients at TH annually, and more than 500 000 persons visit the out patients clinics every year [131]. According to Doctor Ekkekard Zöllner, the majority of the patients are of mixed ancestry ("colored") [127].

At TH, about 92 children/adolescents < the age of 15 years are admitted to the hospital and to the paediatric ward annually, including rehospitalizations. The maximum number of bed in the ward is five [127]. A total of 137 children/adolescents are followed up at the out-patient clinic per December 2010 [132]. The patients are admitted to the paediatric ward until the age of 13 years. According to doctor Zöllner, this age limit can unofficially be extended to 16-17 years depending on the nursing staff [127].

6.2.4. Part 2c. Diabetes mellitus type 1 in Norway

T1D is the second most common chronic condition among children and adolescents in Norway [2]. Approximately 25 000 have T1D. Around 600 Norwegians are diagnosed with T1D every year, about 300 of them are children/adolescents under the age of 15 years. The last 30 years the number of children/adolescents with diabetes has doubled in Norway [133]. Over 2500 children under the age of 15 years have T1D [134]. Norway is one of the countries with the highest incidence of children aged 0-14 years with T1D [133]. The last couple of years one has also seen cases of children developing T2D, but this is still seldom [134].

6.2.4.1 The Norwegian Childhood Diabetes Registry (NCDR)

NCDR is a nationwide, and population-based registry which is including patient data of all children/adolescents < 15 years with newly diagnosed T1D since 1989. One of their main aims is to assess epidemiology in childhood onset-diabetes, with focus on e.g. incidence, prevalence,

long-term complication and mortality. Additionally they assess the quality of diabetes care given at various hospitals in Norway. NCDR received information about new cases of childhood onset diabetes from all pediatric departments in Norway [135]. The patients and their parents/family have to sign a written consent to be included in the registry [2].

6.2.4.2 Diabetes complications in childhood onset type 1 diabetes in Norway

In December 2011, NCDR published the annual report of 2010. During the period 2001- 2010 an average percentage of around 4.7 % of all children/adolescents with T1D were admitted yearly to various hospitals in Norway due to DKA. In 2010, a total of around 18 % of the children/adolescents aged between 0-14 years diagnosed with T1D had DKA at the time of diagnosis. During the same year, the percentage of children and adolescents with T1D who developed severe hypoglycaemia with unconsciousness/convulsions was 6 %. This percentage has decreased annually from 14 % in 2001[2].

When screening for diabetic nephropathy at the annual check in 2010, NCDR registered that out of all those patients with T1D in Norway whom had delivered a urinary test (n= 2041), 10 % had ACR > 2.5 mg/mmol or AER > 20 microgram/min, 0.9% had persistent microalbuminuria, and 0.6 % had proteinuria [2]. In 2007, results from a nationwide Norwegian study were published. They reported that 7.8 % of the participants diagnosed with childhood-onset T1D in 1973-82 had overt nephropathy after a mean duration of 24 years (range 19-30 years). Around 14.9 % had persistent microalbuminuria [136].

The same 24-year follow-up study of 294 children/adolescents with childhood-onset type 1 diabetes (< 15 years of age) showed that 89.1 % of the patients had developed diabetes retinopathy, and the 25-year cumulative incidence of proliferative diabetes retinopathy was 10.9 % [137].

6.2.4.3 Mortality of childhood onset type 1 diabetes in Norway

During the period between 1973 and 2002, a total number of 1906 Norwegian children/adolescents below 15 years of age diagnosed with childhood onset type 1 diabetes (between 1972 and 1982) were followed up, trying to examine the long-term total and cause-specific mortality. The study group estimated that the cumulative survival according to diabetes duration was 98.9 % at 10 years, 98.0 % at 15 years, 96.7 % at 20 years, and 94.6 % at 25 years. A total number of 103 individuals died (25 of the participants emigrated), 42 died because of

diabetes-related conditions. Skrivarhaug et al. found that acute metabolic complications (DKA, hypoglycemia) were the most common cause of death in patients less than 30 years of age (32 %), while CVD was the main cause of death in patients older than 30 years (30 %). This study confirmed that children/adolescents with childhood-onset type 1 diabetes still have an increased risk of dying compared with the general population [138].

6.2.5 Public health and diabetes care in Norway

6.2.5.1 The public health system in Norway

Norway is organized after a welfare model which includes a right to health care for all citizens with residence permit, subsidized higher education, and a comprehensive social security system. The health system is divided into three main level of care; the first-line services, the second-line services and the specialized referral hospitals. The first line services are provided by the GPs, while the second line services are mainly provided by the specialist doctors. The GP refers the patients to the second-line services, or in few cases to the specialized hospitals if necessary.

6.2.5.2 Patient Organizations in Norway

The Norwegian Diabetes Association is an independent, voluntary patient organization for children/adolescents and adults with diabetes. The Organization was founded in 1948 and it is a member of the IDF. Their main goal is to stimulate to diabetes research, and to prevent that people with diabetes have their life-length shortened, or their quality of life reduced because of their disease [139].

6.2.5.3 Stavanger University Hospital in Norway

SUH is a public hospital situated in Stavanger city in the south-western part of Norway. SUH is considered as the fourth largest hospital in Norway due to their level of activity, and they serve a population group of 330 000 people [140].

According to the diabetes nurse Liv Haram at SUH, 30 to 35 patients are being admitted at the pediatric ward annually, including re-hospitalizations. Approximately 20 to 25 new patients are admitted every year. A total of 170 children/adolescents are being followed up at the out-patient at this time. The children/adolescents can be admitted at the pediatric ward until they are 14 years old. After this age they are admitted at the ward of internal medicine. However, the adolescents are being followed up at the out-patient clinic until the age of 16 years from January 2012. Earlier the age-limit was 18 years, but due to lack of capacity they had to reduce it to 16 years [141].

7. Part 3. CASE-STUDY

7.1 RESULTS OF THE QUALITATIVE “FIELD-STUDY”, AND A COMPARISON BETWEEN TYGERBERG HOSPITAL AND STAVANGER UNIVERSITY HOSPITAL CONCERNING DIABETES CARE

Diagnostics

In the majority of cases it is the classical symptoms such as polydipsia and polyuria which makes the patient and his/her parents contact a doctor both at TH and SUH. Additionally the diabetes nurse at TH mentioned tiredness and weight loss as relatively common symptoms. Patients who had developed DKA could also have symptoms like diarrhoea and vomiting. TH and SUH follow ISPADs diagnostic criteria for both diabetes and DKA.

At both TH and SUH it is the doctor, a paediatrician/paediatrician endocrinologist who set and/or confirm the diagnosis of diabetes. From the time of diagnosis it is the specialist health service which has the responsibility for the treatment and follow-up. The patients newly diagnosed with T1D are admitted and treated at the hospital ward. At TH the average length of the stay is one to two weeks. In some cases the patient has to stay at the hospital for as long as one month, depending on the social situation at home. At SUH the common length of stay is one week. After discharge from the ward the children/adolescents with diabetes are followed up at the out-patient clinics at TH and SUH.

At TH most of the patients with T1D had DKA at the time of diagnosis (not given in percentage), while 6 % of the patients at SUH had DKA at diagnosis. Approximately 18.2 % of the newly diagnosed patients with T1D in Norway as a whole had DKA during the same year.

Table 5. Diagnostics of childhood onset type 1 diabetes at Tygerberg Hospital (TH) and Stavanger University Hospital (SUH) together with the guidelines of the International Society for Pediatric and Adolescents Diabetes (ISPAD)

Diagnostics	TH	SUH	ISPAD guidelines
Classical symptoms:	Polydipsia Polyuria	Polydipsia Polyuria	
Diagnostic to set the diagnose of diabetes?	Follow ISPAD guidelines	Follow ISPAD Guidelines	1.Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/L or 2. Fasting plasma glucose ≥ 7.0 mmol/L or 3. 2-hour postload glucose ≥ 11.1 mmol/L during an OGTT
Who usually make the diagnosis?	GP*, but the patients have to be referred to the hospital for confirmation of the diagnosis and treatment.	Specialised Health service. Referred by the GP*.	
Where are recently diagnosed juvenile diabetics treated the first time?	Hospital ward with beds	Hospital ward with beds	
If the patient is admitted to the hospital, what is the average length of stay?	One to two weeks. Sometimes until four weeks.	One week	
Who takes over the responsibility for the treatment and follow-up at the local hospital?	Paediatrician endocrinologist	Paediatrician	
Which diagnostic criteria do you use for DKA?	Follow ISPAD guidelines	Follow ISPAD guidelines	1.Hyperglycemia (blood-glucose ≥ 11 mmol/L 2. Venous pH < 7.3 or bicarbonate < 15 mmol/L 3. Ketonemia and ketonuria

*GP; General Practitioner

Treatment at Tygerberg Hospital

At TH syringes, needles and insulin pens are all available treatment regimens. Approximately 75 % of the patients with T1D use an insulin pen for administration of insulin, while 25 % of the patients use syringes. None of the patients are on treatment with insulin pump. Every patient inject insulin > three times per day. The patients either use a combination of intermediate-acting insulin and rapid-acting insulin or insulin-analogues. Patients who are on treatment with analogues either use a combination of Humalog (insulin lispro) and Lantus or Novorapid and Levemir.

Treatment at Stavanger University Hospital

Syringes, needles, and insulin pens are available at SUH like at TH. Additionally the patients have the opportunity to use an insulin pump for administration of insulin and to measure BG using a continuous subcutaneous glucose monitoring (CSGM).

Table 6. Treatment of childhood onset type 1 diabetes at Tygerberg Hospital (TH) and Stavanger University Hospital (SUH) together with the International Society for Pediatric and Adolescents Diabetes's (ISPAD) recommendations:

Treatment	TH	SUH	ISPAD recommend;
What types of treatment/treatment regimens are available for children with diabetes at the local hospitals?	Syringes Needles Insulin pen	Syringes Needles Insulin pen Insulin pump CSMG*	Pump is the best way of imitating the physiological insulin profile
How many patients use multi injection therapy (>3 injections)	100 %	100%	ISPAD recommend MDI (≥ 4 injections)
What proportion follows the various treatment regimens?	Syringes: 25 % Insulin pen: 75 % Insulin pump: None	Syringes: None Insulin pen: 49% Insulin pump: 51%	
What kind of insulin preparations are used in the multi injection therapy?	Intermediate-acting and rapid-acting insulin or analogues	Intermediate-acting and rapid-acting analogue. Seldom premixed insulin preparations.	Recommend regular and NPH-insulin** as a minimum.

*CSMG; Continuous Subcutaneous Glucose Monitoring, **NPH-insulin; Neutral Protomine Hagedom insulin

Around 51 % of the patients with T1D were on treatment with insulin pump in 2011, and 49 % were using an insulin pen. Among all children/adolescents with T1D in Norway, 59 % were on insulin pump treatment, and 41 % were on insulin pen in 2011 [135].

Every child/adolescent at SUH is on multi injection therapy. Patients on an insulin pump regiment use a combination of intermediate-acting and rapid-acting insulin analogue. According to the diabetes nurse Liv Haram, they seldom offer the patients premixed insulin preparations. However, currently, one child uses this at the moment.

Following up at Tygerberg Hospital (including diabetes education/re-education)

At TH a multidisciplinary team including a diabetes nurse, a doctor, a social worker, and a nutritionist is participating in the treatment and follow up of the children/adolescents diagnosed with diabetes. The multidisciplinary team meet relatively frequently to discuss various patients, and to create a plan to ensure the best possible treatment and following up of the patients. The patient has one/two particular contact persons, either the diabetes nurse or the doctor, or both. After the time of diagnosis the specialist, the pediatrician endocrinologist, has the responsibility of the following up of the patient.

Both the child and the parents receive diabetes education at the time of diagnosis and after discharge from the hospital. Additionally the diabetes nurse Fiona Liebenberg try to involve the staff at the patient`s school, and other persons who have responsibilities concerning the child/adolescent. The hospital has access to an interpreter if the child and his/her parents do not understand English. At the hospital they have one interpreter available. Sometimes it can happen that she is occupied at another ward. Then the diabetes nurse Liebenberg tries to find a nurse who can understand and speak e.g. Xhosa to interpret to the patient/parents.

The diabetes education is both organized by training in groups or/and individual training. The diabetes education is a continuous process over time. After discharge from the hospital the children/adolescents meet up at the out-patient clinic every third months for further training/re-education by the diabetes nurse. The nutritionist at the hospital can offer training in carbohydrate counting depending on the intellectual capacity of the patient/parents. The patients normally come with their parents to the out-patient clinic. The diabetes nurse has the impression that most of the patients are closely followed up by their parents at home. In most cases the re-education is individual organized at the out-patient clinic. Though, at the paediatric ward, if there are several patients from the same age-group they can organize the training in groups. When a patient turn acute ill at home he/she or the parents normally contact the diabetes nurse for council. Sometimes the patients also have the opportunity to talk with the doctor at the ward.

Following up at Stavanger University Hospital (including diabetes education/re-education)

A multidisciplinary team, consisting of a diabetes nurse, a doctor, a school nurse (if possible), a social worker, a nutritionist and a psychiatrist (if needed and if it is desirable for the patient), is participating in the treatment and following up of the children/adolescents with diabetes. One month after the time of diagnosis the diabetes nurse and one of the three nutritionist normally arrange a meeting with the patient and his/her parents to give further information about e.g. nutrition, and carbohydrate counting. A few years ago the nutritionist was only involved in the diabetes education at the time of diagnosis. Now he/she is also involved in the process of following up the children/adolescents. Normally the patients only meet the social worker at the diagnosis. Then they are informed about their economic rights, and opportunity to receive financial help from the Norwegian welfare state.

Every child/adolescent has one contact person, the diabetes nurse Liv Haram. After the time of the diagnosis the endocrinological out-patient clinic take over the responsibility for the following-up of the patients. First of all the patients meet the nurses at the out-patient clinic, but they also meet the doctor. In average they meet the specialist doctor maximum two times per year. In some cases it is the GP who primarily follow up the patient, depending on where the children/adolescents lives, and how far it is to the hospital.

When it comes to who receive the diabetes education it depends on the age of the child. In cases where the child is less than five years old, it is the parents whom are trained. Then they arrange re-education later when the child has become older. When a child is older than five years the diabetes-team try to educate him/her as far as possible, giving him/her customized information. Additionally they train parents, grandparents or other caregivers. If the family/the patient has a near relation to e.g. his/her teacher, or the personnel working in the kindergarten, the diabetes nurse also tries to involve them in the education. They receive information about e.g. injection technique, BG-measuring, and nutrition. Older siblings can also receive some basic information about diabetes.

At SUH they have access to an interpreter if needed. In the majority of cases the interpreter is physically present at the out-patient clinic together with the patient, and the diabetic nurse. In some cases he/she is only available through the telephone. The latter is more challenging.

The patients receive educational training both at the time of admission at the hospital and at the out-patient clinic after discharge. Normally the diabetes education is individualized both at the ward (by a doctor and a diabetes nurse) and at the out-patient clinic (by a diabetes nurse). However,

sometimes they offer training in groups at the ward if several children from the same age-group are admitted at the same time. In some cases, a patient and his/her parents prefer to receive the diabetes education at the out-patient clinic together with another patient and his/her parents because they are familiar with each other. In those cases, the diabetes nurse tries to meet their desire.

Every year, all patients whom are about to start secondary school (around 12 years) and/or their parents are offered to participate in a re-education course, initiated by SUH. The patients and/or their parents receive separated training, but they go through the same topics. A doctor, a nutritionist, and a diabetes nurse are responsible for the training. The patients and/or the parents also have the opportunity to receive additional training at the out-patient clinic if needed.

Table 7. Following-up of patients with childhood onset type 1 diabetes at Tygerberg Hospital (TH) and Stavanger University Hospital (SUH) and the International Society for Pediatric and Adolescents Diabetes's (ISPAD) recommendations

Follow-up	TH	SUH	ISPAD recommends:
Who participate in the treatment and follow up?	A multidisciplinary team (diabetes nurse, doctor, social worker, nutritionist)	A multidisciplinary team (diabetes nurse, doctor, school nurse, social worker, nutritionist, psychiatrist)	A multidisciplinary team (including a minimum of a diabetes specialist nurse and a dietician)
Does the child have one contact person?	Yes, either the Doctor or the Diabetes Nurse	Yes, the Diabetes Nurse	
When the diagnosis is made who is responsible for the follow-up?	The Specialist (Doctor/Diabetologist)	The Specialist (Doctor, Diabetologist), and the Diabetes Nurse	
Who are educated?	The patient, parents/other caregivers, the school etc.	The patient, parents/other caregivers, school, etc.	
Access to interpreter?	Yes	Yes	
How is the education organized?	Individual and in groups.	Individual and in groups.	
When is a new education organized?	Continuously education. Every third month	Continuously. Re-education course after age 12 years, and when needed.	Continuously education

As part of the diabetes education the children/adolescents are trained in carbohydrate counting. In December 2010 SUH had only practiced this for around a year.

Up until the children/adolescents are around 12 years of age, the parents normally participate in the

consultation/education. When the patients have turned 12 years old and up to 16 years they try to encourage the patient to talk with the diabetes nurse alone at the start of the consultation, where-as the parents are included at the end of the consultation. When the adolescents are ≥ 16 years, the patients can choose themselves whether their parents should be present or not.

When a child turns acutely ill at home, the patient/parents either take contact with the diabetes nurse, the paediatric ward, the emergency room, or the GP (if it happens during daytime).

Treatment goals

Both TH and SUH are adhered to the treatment goals of ISPAD, which is an HbA1c < 7.5 %.

According to the diabetes nurse Haram at SUH around 33 % of the patients achieved the treatment goals in 2010. Among these patients one can also find children/adolescents with newly diagnosed diabetes who still have some self-production of insulin. Thus, the BG can be easier to control.

Around 26 % of all the children/adolescents with diabetes in Norway achieved an HbA1c < 7.5 % in 2011. At TH they started to register the number of patients and their HbA1c in August 2010.

Patient data from the period between August and December 2010 was received. During that period 9 % of the patients achieved an HbA1c < 7.5 %.

At TH the children/adolescents with T1D attend diabetes check-ups every one to three months.

Normally they come every third months, but if the diabetes team has an impression of poor control (HbA1c > 14 %) they prefer to see the patients more frequently. During the diabetes check-up at TH they measure BG, HbA1c, weight, and compare the BG written down in the patients BG-diary with the BG levels measured by the BG-meter. They check for any infection around the injection site.

At SUH the patients attend diabetes check-ups one, and then two weeks after the time of diagnosis. When the children/adolescents and/or their parents have become more capable of managing the disease themselves, they come every third months. During the period between two weeks and three months after the diagnosis they have the opportunity to come to another check-up at the out-patient clinic if needed.

Most of the patients attend their appointments both at TH and SUH (not given any percentage).

Table 8. Treatment goals concerning childhood onset type 1 diabetes at Tygerberg Hospital (TH) and Stavanger

University Hospital (SUH) and the International Society for Pediatric and Adolescents Diabetes`s (ISPAD) guidelines.

Treatment goals	TH	SUH	ISPAD guidelines
What are the treatments-goals at age < 18 years?	HbA1c* < 7.5 %	HbA1c* < 7.5 %	HbA1c* < 7.5 %

*HbA1c; Hemoglobin A1c

Complications/associated autoimmune diseases

Both TH and SUH have a routine screening program for autoimmune diseases and late complications. At TH the patients are screened for hypo- and hyperthyroidism annually, and for celiac disease every second year. At SUH they perform screening for both thyroid disease and celiac disease annually. Additionally the patients are screened for late complications (retinopathy, nephropathy, neuropathy and angiopathy) annually at both hospitals.

As mentioned, acute complications due to diabetes are hypoglycaemia and DKA. According to the diabetes nurse at TH they hardly newer see patients hospitalized due to severe hypoglycaemia with unconsciousness and/or convulsions (not given any exact percentage), because they have trained the parents to be aware of and treat hypoglycaemia at home. Then the parents can bring the child to the hospital after he/she has been stabilised with a higher BG. During the period between August and November 2010, 28 patients had DKA out of a total patient group of 171 individuals. This is equal to an average percentage of 16.4 %. At SUH, 15 patients were admitted because of severe hypoglycemia in 2010, which accounts for 8.8 % of the total patient-group. Approximately 3.5 % of the patients were admitted due to DKA (n=6).

The incidence (%) of long-term complications among children under the age of 15 years is according to Haram at SUH nearly similar to none. She has experienced one or two cases of patients with diabetes retinopathy. Currently, one of the patients at SUH receives treatment for HT and hypercholesterolemia at the Oslo University Hospital, and one of the patients has nephropathy (his/her mother also have a kidney disease). Unfortunately the personnel at TH were not able to give me information about the percentage of long-term complications among their patients.

Table 9. Screening for autoimmune diseases in children with type 1 diabetes at Tygerberg Hospital (TH) and Stavanger University Hospital (SUH) and the International Society for Pediatric and Adolescent`s (ISPAD) guidelines

Screening for autoimmune diseases	TH	SUH	ISPAD guidelines
Celiac disease	Every second year	Annually	At the time of diagnosis. Then annually first five years. Every second year thereafter (if asymptomatic patient)
Hypo-/hyperthyroidism	Annually	Annually	At the time of diagnosis. Then every second year (if asymptomatic patient)

Table 10. Screening for late complications in children with type 1 diabetes at Tygerberg Hospital (TH) and Stavanger University Hospital (SUH) and the International Society for Pediatric and Adolescent`s (ISPAD) guidelines

Screening for late complications	TH	SUH	ISPAD guidelines
Retinopathy	Annually	Annually	Annually from age 11 years with after 2 years duration and from 9 years with 5 years duration
Nephropathy	Annually	Annually	Annually from age 11 years with 2 years duration and from 9 years with 5 years duration
Neuropathy	Annually	Annually	Unclear
Macrovascular disease	Annually	Annually	After age 12 years

8. DISCUSSION

Both TH and SUH follow the ISPAD guidelines in their diabetes care. Principally the two hospitals were able to put into practice most of the ISPAD recommendations both including the diagnostic criteria for diabetes and DKA, treatment, treatment goals, following-up of the patients, and screening for autoimmune diseases and late-complications. The following discussion will focus on the aspects of the diabetes care which actually differed between TH and SUH, with an effort to compare parts of the diabetes care in SSA with the diabetes care in SA.

Diagnostic criteria/treatment targets

Every hospital and/or health clinic needs to have access to diagnostic equipment, such as a BG-meter and HbA1c-monitoring, to be able to set the diagnosis of diabetes and to be able to follow-up patients with T1D in an adequately way. According to various studies done in SSA and in Africa as a whole, this is often insufficiently or -unavailable in many of these countries. According to ISPAD, BG-monitoring can be very expensive. This can explain why such equipment can be unavailable in many countries in SSA where the state economy might be poor, or/and they have to face other health challenges. A frequent measuring of the BG-level is important to improve HbA1c and to reach treatment goals. However, this can be difficult to achieve in many countries/health institutions in SSA, where they do not have sufficient access to equipment to measure the BG. At TH, they have the opportunity to equip their patients with both syringes and home blood glucose meters, among other materials (needles, insulin pen, blood glucose test strips, lancets for finger-pricking, and urine sticks to check for ketonuria), since the government is partly financing all the materials. Thus, they have the opportunity to follow the ISPAD's diagnostic criteria for diabetes and include frequent monitoring of BG as part of the diabetes treatment as recommended by ISPAD. In other countries in SSA, where the equipment is not sufficient available or lacking, the importance of a good clinician is even more essential for diagnosis.

Monitoring of HbA1c has been shown to be a very important factor in the diabetes care. An HbA1c-monitor is rarely available at health institutions in countries in SSA. This makes it impossible to measure the patients HbA1c-value once per year as recommended by ISPAD as a minimum. However, at TH, they have the opportunity to monitor the HbA1c of every patient, and this is performed at a frequent level, equal to SUH. According to ISPAD, the treatment goal should be $HbA1c < 7.5 \%$. Even in developed countries with strong health-economy this can be hard to achieve. A larger percentage of the patients at SUH achieved this treatment goal compared to at TH. This might portray a real difference. However, it is not certain that those patients coming to the out-patient clinic at TH during the period between August and December were representative to the

whole patient-group coming to the hospital in 2010. This makes it hard to draw any firm conclusion.

Both TH and SUH followed the ISPAD guidelines concerning the diagnostic criteria for DKA. Most of the patients at TH had DKA at the time of diagnosis, while 6 % had DKA at SUH. This can represent a real difference. However, it can be problematic to make a conclusion, since the estimate from TH is not based on systematically registered patient data for the year 2010 in total. Another aspect which showed a discrepancy between SUH and TH was that the average length of stay when a patient was admitted at TH was longer than that at SUH. In those cases where the patients had to be as long as two to four weeks at TH, this was primarily due to a difficult situation at home, or children/adolescents and their parents being illiterate [132]. In these cases it was necessary to keep the patients longer to be sure that they were able to manage to e.g. measure the BG themselves, and to inject insulin.

Treatment

Children/adolescents with T1D are dependent on insulin for survival. According to ISPAD they should as a minimum have access to adequate amounts of regular and intermediate-acting insulin (NPH-insulin). However, various studies show that insulin is often unavailable in many countries in SSA due to different factors. At TH, insulin, glucagon, and anti-diabetic drugs are fully financed by the public health care system. Thus, the children/adolescents with T1D at TH have access to sufficient insulin. Additionally at TH, they have the ability to offer their patients insulin analogues as recommended by ISPAD.

As mentioned, ISPAD recommend a MDI- treatment regiment. All patients (100%) at TH and SUH were on a MDI-regiment. In many countries in SSA and in Africa as a whole this is often impossible to achieve when they do not have access to either adequate insulin, or injecting devices.

Insulin pumps, and insulin pens are more expensive methods of administrating insulin than syringes. Thus, these types of devices are unavailable in many developing countries, such as in SSA. Insulin pens were available at TH, while insulin pumps were not. The most likely reason for this is that the public health care system financed the use of insulin pens, but not the insulin pumps. At SUH a large percentage of the patients with T1D were on insulin pumps.

Follow up/education and/or re-education

A frequent and high level of educational input, and a continuously following up and reeducation is fundamentally important to obtain a good diabetes care. Some studies from different African

countries have reported that one of the major challenges concerning diabetes care has been the lack of following-up, where either the number of qualified health personnel is few, or they are not sufficiently trained in diabetes care. At TH, a multidisciplinary diabetes team participates in the treatment and following up of patients with T1D. The diabetes education is performed at the time of diagnosis, and on a continuously basis like recommended by ISPAD.

Complications/associated autoimmune diseases

Studies which have been done in countries in SSA showed that < 50 % of the individuals knew that they had diabetes. However, in SA, the number of patients being aware of their disease (in urban areas) was comparable to the percentage in many of the developed countries. If health institutions in SSA do not have sufficient access to equipment to diagnose diabetes, they probably do not either have adequate equipment to screen for complications. At TH, the screening program was organized like ISPAD recommended. One factor that differed between TH and SUH was that SUH performed screening for celiac disease annually, while TH performed the same screening every second year (though not specified the diabetes duration at either TH nor SUH). The reason for this is not known. It could perhaps be explained by the more practical aspect of it. Annually screening for every disease is easier to perform, than trying to remember when they did the screening for celiac disease the last time.

Since the personnel at TH started to register patient data systematically from August 2010 it was difficult to compare specific patient data with the one received from SUH concerning acute-complications. However, out of the data received, it appeared that a much larger number of patients had DKA at the time of diagnosis at TH compared to at SUH. This was also the situation when it came to the number of patients developing DKA after the time of diagnosis. According to the personnel at TH, patients were seldom admitted due to severe hypoglycaemia (with unconsciousness and/or convulsions). However, it was difficult to give an exact percentage of how many. At SUH, 8.8 % of the patients were admitted due to this. The percentage of patients at SUH developing late-complications was very low. Unfortunately, the personnel at TH did not have the opportunity to give any percentage of how many of the patients who had developed late-complications. Therefore it is impossible to compare data on late-complications between TH and SUH. This is a weakness of this thesis.

General comments on collection of data in relation to this thesis

In SSA and SA, scientific articles about diabetes care, T1D in general, and especially T1D among children/adolescents aged between 0 to 14 years, are relatively scarce. Sometimes, this made it

necessary to include a larger geographical area to find more information, like Africa as a whole. In some cases it was not possible to have access to full-text studies and articles done in SA, and SSA. Therefore it was necessary to refer to some of the abstracts in this thesis.

Few studies on diabetes complications, and mortality among children/adolescents with T1D aged between 0 and 14 years have been performed in SSA, and SA. Most of the studies on acute- and late complications among individuals with diabetes do not separate between patients with T1D and T2D, nor do they specify the age of the patient-group participating. In this thesis, only studies that clearly involved also young people under the age of 15 years, and T1D, were referred to.

When searching for relevant data, mainly PubMed has been used. Thus, it is possible that information from other relevant studies/articles have not been included in this thesis.

9. CONCLUSION

SA is part of SSA/Africa geographically. However, SA is not representative for this region in many ways. In 2011, SA had an HDI which placed the country above the regional level [82]. This reflects a higher level of health care, education, and income compared to most of the other countries in the region. Thus, it might not be surprising that the diabetes care appeared to be of a higher quality at TH (and SA) compared to the diabetes care given in many of the other countries in SSA. After having studied various papers describing diabetes care in SSA, the overall impression was that most of the countries struggled to be able to offer sufficient healthcare to the patients with diabetes, due to various reasons. This was not representative for the situation at TH, which appeared to be well-functioning based on the information received by interviewing the health personnel at this hospital. This form a sharp contrast to what a fellow medical student found during her case study about diabetes care in Rwanda [142].

In this thesis diabetes care at TH in SA was compared to the diabetes care given at another public university hospital, SUH in Norway. Norway has the highest HDI in the world [82], and the quality of the diabetes care at SUH is comparable to the diabetes care given at other hospitals in Norway. Even though the economic situation might differ, the diabetes care at TH seemed to be comparable to the diabetes care given at SUH in most ways. However, it is important to point out that this conclusion is only based on the information received by interviewing health personnel at both places. Unfortunately, patient data from TH is partly missing. This makes it difficult to draw any firm conclusion about the quality of the diabetes care at TH compared to the diabetes care at SUH. The fact that TH first started registering patient data systematically some months before visiting the

paediatric ward might give an impression that TH has had less focus on diabetes-related complications earlier, but it can also be due to e.g. less available resources at TH compared to at SUH.

It is also important to point out that TH is only one out of several public hospitals in SA. Therefore it is not possible to make generalizations about the diabetes care in SA as a whole. Data about diabetes management in SA is scarce. It is known that SA is still not capable of achieving adequate health care for all South- Africans in general, and the fact that they did not have a national diabetes registry show that the focus on diabetes care is still not satisfactory enough. The health care given at TH is probably above the average level in SA. Additionally, TH was situated in the province with the highest life expectancy rate in SA, and this might reflect that the health care given at TH is of better quality than health care given at a hospital in another region.

This “case-study” from TH represents something positive, and the diabetes care at TH might serve as a model for other health personnel and health institutions in SA, and in SSA/Africa as a whole. Additionally, during the recent years, there has been an increasing focus on diabetes in SSA/Africa as a whole, and how to achieve better diabetes care for the many patients. Hopefully this will result in better health care for the individuals with diabetes in SSA/Africa in the nearest future.

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12. APPENDIX

QUESTIONNAIRE – DIABETES (T1D and T2D) IN CHILDREN: A GLOBAL PERSPECTIVE 17.11.10

The questionnaire is designed to gather information about children with diabetes ≤ 15 years of age. The interview is in two parts. Each part should not last more than 1 hour.

The first part is designed to map diabetes in children at a national or regional level. Each country has a number code (see list). The regions/counties/states are indicated by names. The interviewer fills out this first part of the interview based on information available on the internet and other available sources. The information will then be quality assessed with the local informant.

The second part is designed to map how children with diabetes are followed up at the local hospital/treatment centre. The interview contains multiple open, qualitative questions. The interview will therefore be tape-recorded. The tape recordings will be transcribed before the analysis takes place.

The questionnaire does not ask for personal sensitive information.

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Country (code):
Region/county/state:
Date:
Informant: name/occupation
Interview by:

PART 1

Incidence

1. The annual incidence of the different types of diabetes in this country (enter the number and percentage)
 - Type 1 diabetes (T1D)
 - Type 2 diabetes (T2D)
 - Gestational diabetes
2. The incidence of T1D and T2D among children under 15 years of age
 - The total incidence:
 - How is the distribution in the following groups of ages (estimated):
 - <5 years
 - 5-<10 years
 - 10-<15 years
 - > 15 years
3. What is the gender distribution among children with T1D and T2D in the country?
4. What are the overall proportions of the following ethnicities in this country:
 - White / European background (non-Hispanic whites)
 - Black / African background
 - Middle-East / North-African
 - Indian subcontinent
 - East-Asia
 - Middle- and South American (Hispanics)
 - Indigenous (specify)
 - Mixed (or unclassified)
5. How many children with diabetes in this country are
 - White / European background (non-Hispanic whites)
 - Black / African background
 - Middle-East / North-African
 - Indian subcontinent
 - East-Asia
 - Middle- and South American (Hispanics)
 - Indigenous (specify)
 - Mixed (or unclassified)

Prevalence

6. What is the prevalence of T1D and T2D among children in the following groups of age?
- <5 years
 - 5-<10 years
 - 10-<15 years
 - ≥ 15 (adults)

Mortality

7. What is the average life expectancy in the country?
- Women:
 - Men:
8. What is the average life expectancy among patients diagnosed with T1D before the age of 15?
- Women:
 - Men:

National health

9. How many doctors per citizen? (This will differ depending on location; city, rural, town etc)
10. Is there a geographical difference in availability of doctors?
11. What is the gross domestic product (GDP) of the county?
12. What is the total expenditure on health as a percentage of the GDP?
- Which proportion is financed by the public?
 - Which proportion is financed by private actors?
13. Which proportion of the national budget is spent on health?
14. Does the public health care system finance the costs associated with diabetes medication and equipment?
- Yes
 - No
15. If the answer is yes on question 14, which *medication* is financed?
- Insulin
 - Yes
 - _____% financed
 - No
 - Antidiabetic drugs
 - Yes
 - _____% financed
 - No

Glucagon

- ☐ Yes _____% financed
- ☐ No

16. If yes on question 14, which of the following *materials* is financed

- ☐ Syringes:
- ☐ Needles:
- ☐ Insulin pen:
- ☐ Insulin pump:
- ☐ Materials for the insulin pump: (needle, catheter, reservoir etc):
- ☐ Home Blood Glucose meters:
- ☐ Blood glucose test strips:
- ☐ Finger-pricking devices:
- ☐ Lancets for finger-pricking:
- ☐ Continuous subcutaneous glucose monitoring devices:
- ☐ Urine sticks to check for ketonuria:
- ☐ Other:_____

17. If the answer is yes on question 14, does the patient have to pay anything? If so, how much? (%)

- ☐ Syringes:
- ☐ Needles:
- ☐ Insulin pen:
- ☐ Insulin pump:
- ☐ Materials for the insulin pump: (needle, catheter, reservoir...):
- ☐ Home Blood Glucose meters:
- ☐ Blood glucose test strips:
- ☐ Finger-pricking devices:
- ☐ Lancets for finger-pricking:
- ☐ Continuous subcutaneous glucose monitoring devices:
- ☐ Urine sticks to check for ketonuria:
- ☐ Other:_____

18. Who brings the child to their check-ups?

- ☐ Mum
- ☐ Dad
- ☐ Other:_____ (specify)

19. Are there any laws/public rights for parents to get extra time off work to take their children to check ups?

- ☐ Yes
- ☐ No

20. Are parents with chronic ill children allowed to take additional days off compared to the general population?

- ☐ Yes (_____number of additional days)
- ☐ No

21. Are there national guidelines for the management of children with T1D and T2D?

- ☐ Yes

- ☐ No

Patient organizations

22. Are there any national organizations for patients with diabetes?

- ☐ Yes
 - ☐ For children?
 - ☐ For children and adults?
 - ☐ For adults only?
- ☐ No

23. Are there any local organizations for patients with T1D?

- ☐ Yes
 - ☐ For children?
 - ☐ For children and adults?
 - ☐ For adults only?
- ☐ No

Comment:

24. What do the patient organizations offer the children and their parents?

- ☐ Websites
- ☐ Telephone
- ☐ Courses
- ☐ Information meetings
- ☐ Holiday offers / camps
- ☐ Other:_____

Register for diabetes

25. Is there a national diabetes register?

- ☐ Yes, for children
- ☐ Yes, for adults
- ☐ Yes, for adults and children
- ☐ No

26. If yes, what data is registered? Does it include both T1D and T2D?

Complications

27. What is the incidence of acute diabetes complications among children under 15 years of age?

- ☐ Diabetic ketoacidosis (with hospitalization)
- ☐ Severe hypoglycemia (unconscious with or without convulsions)

28. What is the incidence of late diabetes complications among children under 15 years of age? (estimated percentage)
- Retinopathy
 - Nephropathy
 - Neuropathy

Country (code):
Region/county/state:
Local treatment center (name and type):
Date:
Informant: name/occupation
Interview by:

PART 2

Hospitalizations and number of hospital beds

29. How many children <15 years with diabetes are admitted to hospital annually in the following wards (The total number of hospitalizations including rehospitalization)
- ☐ Paediatric ward
 - ☐ Adolescents ward
 - ☐ Internal medical ward
30. To what age are the children managed in the paediatric wards? _____
31. If there is an adolescent department, when do the children start attending and how long can they attend there?
32. What is the maximum number of beds in the ward? _____
33. How often has the ward been full during the last 6 months? (regardless of the reason for the hospitalisation)
34. How many children with diabetes are followed up at the local hospital today?
35. How is the gender distribution among the children that are followed up at the local hospital?
36. Who takes over the responsibility for the treatment and follow-up after the diagnosis of diabetes?
- ☐ Specialist _____ (which type)
 - ☐ General practitioner (GP)
 - ☐ Other : _____

Diagnostics

37. Who usually make the diagnosis?
- ☐ General practice
 - ☐ Specialised health service
 - ☐ Nurse
 - ☐ Other: _____

38. What is the average age at diagnosis?

39. What are the classical symptoms that make the patient and his or her parents contact a doctor?

40. Which diagnostic criteria have to be fulfilled to set the diagnose of diabetes?

T1D

- International guidelines; ISPAD (Blood glucose)
- Other guidelines:_____

T2D

- International guidelines; ISPAD (Blood glucose)
- Other guidelines:_____

41. Where are recently diagnosed juvenile diabetics treated the first time?

T1D

- Out-patients clinic
- Hospital ward with beds

T2D

- Out-patients clinic
- Hospital ward with beds

42. If the patient is admitted to hospital, what is the average length of stay?

T1D:

T2D:

43. Which diagnostic criteria do you use for DKA?

- Hyperglycemia
- Standard Bicarbonate (< 15 mmol)
- pH (< 7,3)
- Ketonuria / ketonemia

44. What proportion of children has DKA at diagnosis?

T1D:

T2D:

Treatment and follow up

45. Who participates in the treatment and follow up of children with diabetes?

- Nurse

- ☐ Doctor
- ☐ School nurse
- ☐ Social worker
- ☐ Nutritionist
- ☐ Psychologist
- ☐ Other:_____
- ☐ Multidisciplinary team

46. Does the child with diabetes have one particular contact person? If yes, specify:

- ☐ Yes:_____
- ☐ No

47. When the diagnosis is made who is responsible for the follow-up?

- ☐ Specialist (doctor / diabetologist)
- ☐ Hospital doctor
- ☐ Nurse
- ☐ General practitioner
- ☐ Other:_____

48. Who are educated (at the time of the diagnosis, and after discharge)?

- ☐ The child
- ☐ Parents
- ☐ School
- ☐ School nurse
- ☐ Nursery
- ☐ Activity leaders/coaches
- ☐ Others:_____
- ☐ No one

49. Does the hospital have access to interpreters when they have patients that do not speak/understand English?

50. How is the education organized?

- ☐ Training in groups
- ☐ Individual training
- ☐ A combination of both

51. When is a new education organized? (re-education)

52. Is carbohydrate counting used systematically when calculating the insulin bolus in relation to food?

53. How is the education organized?

- ☐ Training in groups
- ☐ Individual training
- ☐ A combination of a and

Comment:

54. How much do parents participate in the treatment and follow up?

55. Do the adolescents get contraceptive counselling?
- ☐ Yes (comment ;) _____
 - ☐ No
56. Have you experienced unintended pregnancies in this group of patients?
- ☐ Yes (how many? what are the characteristics of these patients; ethnicity, socioeconomic status etc?)
 - ☐ No
57. What types of treatment/treatment regimens are available for children with diabetes at the local hospital?
- ☐ Syringes
 - ☐ Needles
 - ☐ Insulin pen
 - ☐ Insulin pump
 - ☐ Continuous Subcutaneous Glucose Monitoring
 - ☐ Others: _____
 - ☐ None
58. How many patients use multi injection (insulin > 3 times a day) therapy?
59. What proportion of the patients (in number and percentage) follow the different treatment regimens listed
- ☐ Insulin pump:
 - ☐ Others:
 - ☐ None:
60. Among the children under multi injection therapy what type of insulin preparations are used? (%)
- ☐ Premixed insulin preparations
 - ☐ Intermediate-acting insulin + rapid-acting insulin
 - ☐ Analogues
 - ☐ Which combinations: _____
 - ☐ Are there any different strategies for insulin therapy concerning the child's age?
61. Who does the patient and his or her parents contact if the child is acute ill?
- ☐ Specialist
 - ☐ Contact person
 - ☐ GP
 - ☐ Emergency room
 - ☐ Other: _____

Treatment goals

62. Are the ISPAD treatment goals adhered to?
(ISPAD = International Society for Paediatric and Adolescent Diabetes)
- ☐ Yes

- No
 - If no, which guidelines are used_____

63. What are the treatment goals

- HbA1_c < 7,5 %
- Other:_____

64. What proportions (%) of patients achieve the treatment goals?

65. How often do the children attend diabetes health check ups?

T1D: _____ *T2D:*_____

66. What proportions (%) of the patients attend their appointment?

- Most patients
- 50 %
- Only a few

67. Who does not attend? Why? What are the characteristics of these patients?

68. Is there a screening program for autoimmune diseases?

- Yes
- No

69. If yes, witch diseases are included in the screening

- Celiac disease
- Hypothyroidism / hyperthyroidism
- Others:_____

70. If yes, how often is the screening performed

- At each check up
- Annually
- Other:_____

71. Are there any screening program concerning late diabetes complications among children with diabetes?

- Yes
- No

72. If yes, what kind of late diabetes complications are included in the screening program among children with diabetes? And which methods are used in the screening

- Retinopathy:_____
- Nephropathy:_____
- Neuropathy:_____
- Angiopathy:_____

- Others: _____

73. If yes on question 70, how often is the screening performed

- At every check up:
- Annually:
- Other: _____

Quality of life and mental health:

74. What assistance do the children with diabetes and their parents receive in relation to:

- School
- Hobbies
- Sports

75. Are there social activities arranged for the children and their parents?

76. What kind of social activities are arranged? And who organises them?

77. Have you conducted/do you conduct research on the quality of life in the children with diabetes?

- Yes
 - If yes, can you elaborate
- No

78. Are intoxicants a problem among children with T1D and T2D?

- Yes
 - What kind of intoxicant?
 - What are the characteristics of these patients (gender, ethnicity, socioeconomic status etc)
- No

Comment:

Complications

79. What is the incidence (percentage) of acute diabetes complications among children with T1D and T2D under the age of 15?

Type 1 diabetes

- Diabetic ketoacidosis
- Severe hypoglycaemia with unconsciousness and/or convulsions
- Other: _____

Type 2 diabetes

- Diabetic ketoacidosis
- Severe hypoglycaemia with unconsciousness and/or convulsions
- Other: _____

80. What is the incidence (%) of long-term complications among children under the age of 15 years?
And how old are they?

Type 1 diabetes

- Retinopathy:
How many have been treated with laser?
- Nephropathy:
- Neuropathy:
- Hypertension
How many get anti hypertension treatment?

Type 2 diabetes

- Retinopathy:
How many have been treated with laser?
- Nephropathy:
- Neuropathy:
- Hypertension
How many get anti hypertension treatment?

81. What is the incidence (%) of long-term complication among adults who got the diagnose of diabetes before they turned 15 years?

Type 1 diabetes:

Type 2 diabetes:

The following must be discussed:

- How old were the patients when they where diagnosed with diabetes?
- How many years diabetes duration at onset of the late complication?
- Retinopathy:
- Nephropathy:
- Neuropathy:

82. Is overweight a problem among children with diabetes?

Type 1 diabetes

- If yes:
 - Are there any differences between gender, ethnicity, socioeconomic background etc?
 - In which group is the prevalence of overweight highest?
 - What kind of prevention and treatment regimens does the hospital have?
 - Are the treatment regimens effective?

- Do children with overweight in practice have significant more complications than children with normal weight?
- Are there other problems related to overweight and diabetes?

Type 2 diabetes

- If yes:
 - Are there any differences between gender, ethnicity, socioeconomic background etc?
 - In which group is the prevalence of overweight highest?
 - What kind of prevention and treatment regimens does the hospital have?
 - Are the treatment regimens effective?
 - Do children with overweight in practice have significant more complications than children with normal weight?
 - Are there other problems related to overweight and diabetes?